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Request for grant of a patent

1. Your Reference
   32/64087GB

2. Patent Application Number
   0207529.9
   2 APR 2002

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)
   Norbrook Laboratories Limited
   Station Works
   Newry, BT35 6JP
   County Down
   NORTHERN IRELAND

   Patents ADP number (*if known*) 6141315001

   If the applicant is a corporate body, give the country/state of its incorporation: United Kingdom

4. Title of the invention
   Injectable veterinary composition for small animals

5. Name of Agent
   FITZPATRICKS

   "Address for Service" in the United Kingdom to which all correspondence should be sent
   4 West Regent Street
   Glasgow
   G2 1RS

   Patents ADP number 00000695002

6. Priority Details

Country	Priority Application Number	Date of filing

7. If this application is divided or otherwise derived from an earlier UK application give details

Number of earlier application	Date of filing

8. Is a statement of inventorship and or right to grant of a patent required in support of this request?:

Patents form 1/77

9. Enter the number of sheets for any of the following items you are filing with the form.

Continuation Sheet for this form

Description	4
Claims	0
Abstract	0
Drawings	1

10. If you are also filing any of the following state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a Patent (*Patents Form 7/77*)

Request for Preliminary examination and search (*Patents form 9/77*)

Request for Substantive Examination (*Patents Form 10/77*)

11. I/We request the grant of a patent on the basis of this application

Signature FITZPATRICKS Date: 29 March 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Eric Ede
0141 306 9000

0032782 29-Mar-02 02:48

Injectable veterinary composition for small animals

This invention relates to the use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly the formulation of such drugs in solutions suitable for injection, especially for use in veterinary medicine for the purposes of treating small animals, such as companion animals.

Background of the Invention

Non-steroidal anti-inflammatory drugs find wide application in the treatment of inflammatory conditions and the alleviation of pain in veterinary and human medicine. Such drugs are often characterised by the presence of a carboxylic acid function or derivative thereof. Examples of such non-steroidal anti-inflammatories include carprofen, ibuprofen, ketoprofen, benoxaprofen, naproxen, sulindac, zomepirac, fenclofenac alcofenac, ibufenac, flunixin and indomethacin. The administration of such compounds parenterally can present the difficulty of local irritation and induce haemolytic side effects.

In EP-A-0 280 887, Ferro and Steffen teach the formulation of NSAIDs, by utilising salts of cholanic acid and certain lipids to form mixed micelles in aqueous systems. These compositions have reduced side effects, in comparison with conventional formulations, when administered by injection to dogs.

Objects of the Invention

It is an object of the present invention to provide novel pharmaceutical preparations of non-steroidal anti-inflammatory drugs suitable for injection. It is a further object of the invention to provide such preparations adapted for the provision of analgesia in small animals, especially companion animals.

Summary of the Invention

It has been surprisingly found that NSAIDs, preferably carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a salt thereof, most preferably carprofen in the form of its arginine or lysine salt, can be readily formulated in aqueous systems by the use of certain pharmaceutically acceptable synthetic polymer agents to the effect that the problems of local

irritancy and haemolysis associated with conventional formulations of these drugs are avoided or at least greatly reduced.

Accordingly, the aforesaid objects are achievable by this invention which provides an injectable aqueous composition for veterinary use containing an effective amount of a non-steroidal anti-inflammatory compound together with a physiologically acceptable oxygenated polymeric surfactant.

An additional technical benefit in comparison with formulations utilising the prior art cholanic acid/lipid solubilising method is also achieved by the present invention which offers enhanced stability at room temperature.

Polyoxypropylene/polyoxyethylene block co-polymers (poloxamers) or derivatives thereof are the preferred polymeric agents used for the purposes of the invention as illustrated in the following example for a composition containing carprofen or physiologically acceptable salts thereof as the active ingredient. Such a solution is especially useful in veterinary medicine for a variety of analgesic, anti-pyretic, and anti-inflammatory purposes such as the treatment of, musco-skeletal and visceral pain in horses, pre-and post-operative pain in cats and dogs and of acute inflammation associated with respiratory disease.

The amount of NSAID that can be accommodated in the injection solutions of the present invention can vary over wide limits, for example from 0.5 to 30% by weight, depending on the required dose for effective treatment of the subject. The quantity of poloxamer can also vary over wide limits, for example 0.5 to 20% by weight, the upper limit for a given formulation being determined by viscosity considerations. For practical use the solution should preferably be capable of being readily administered by conventional hypodermic syringe.

The present invention provides another means of formulating NSAID's in aqueous solution, in a form that is suitable for parenteral administration to animals or humans, especially companion animals such as cats and dogs. The compositions of the present invention provide simpler formulations than those of EP 0 280 887, without the requirement for lipids and cholanic acids. It is a further feature of these simpler formulations that they

can be stored at room temperature, contrasting with the cholanic acid/lipid formulation, which typically requires refrigerated storage (2-8 C).

Mode for Performance of the Invention

The invention will now be described further by way of illustrative example with reference to the accompanying Figure, which represents data showing the mean levels of carprofen found in the blood plasma of dogs following administration of a formulation of the invention.

Example

A suitable formulation of carprofen, in this embodiment provided as its arginine salt, can be made by bringing together, following standard industry procedures, the following ingredients to form a mixture which is brought up to injection volume by addition of an appropriate amount of water for injection:

Carprofen 5.0% w/v
L-Arginine EP 3.1% w/v
Lutrol F68 (poloxamer 188, NF, EP) 5.0% w/v
Nipagin M (BP, EP, USP/NF) 0.15% w/v (preservative)
Water for injection *ad* 100% w/v

A comparison was made with the prior art formulation (derived from EP 0 280 887) that uses about 26% by weight, of cholanic acid and lecithin, in a similar strength carprofen formulation. This formulation demonstrates bioequivalence to the aforesaid cholanic acid/lipid formulations but utilises only 5% by weight of the inventive polymeric surfactant additive. Thus compositions of the present invention can substantially reduce the burden of auxiliary ingredients injected into the subject on treatment. These formulations have also been found to have low side effects, with no injection site reactions such as swelling, hardness, softness, heat, redness or pain being observed during studies involving dogs.

A further benefit of compositions according to the invention is that of room temperature stability. A trial lot of the formulation given in the example has been studied over a period of eleven months at ambient temperatures without loss of potency being

observed. The trial lot was assayed as containing 5.16% carprofen on manufacture, 5.10% after seven months, and 5.26% after eleven months, these apparent differences being accounted for by slight moisture loss. Currently available formulations typically require controlled chilled storage at 2-8 C, i.e. refrigeration, cool room, or chiller cabinet storage.

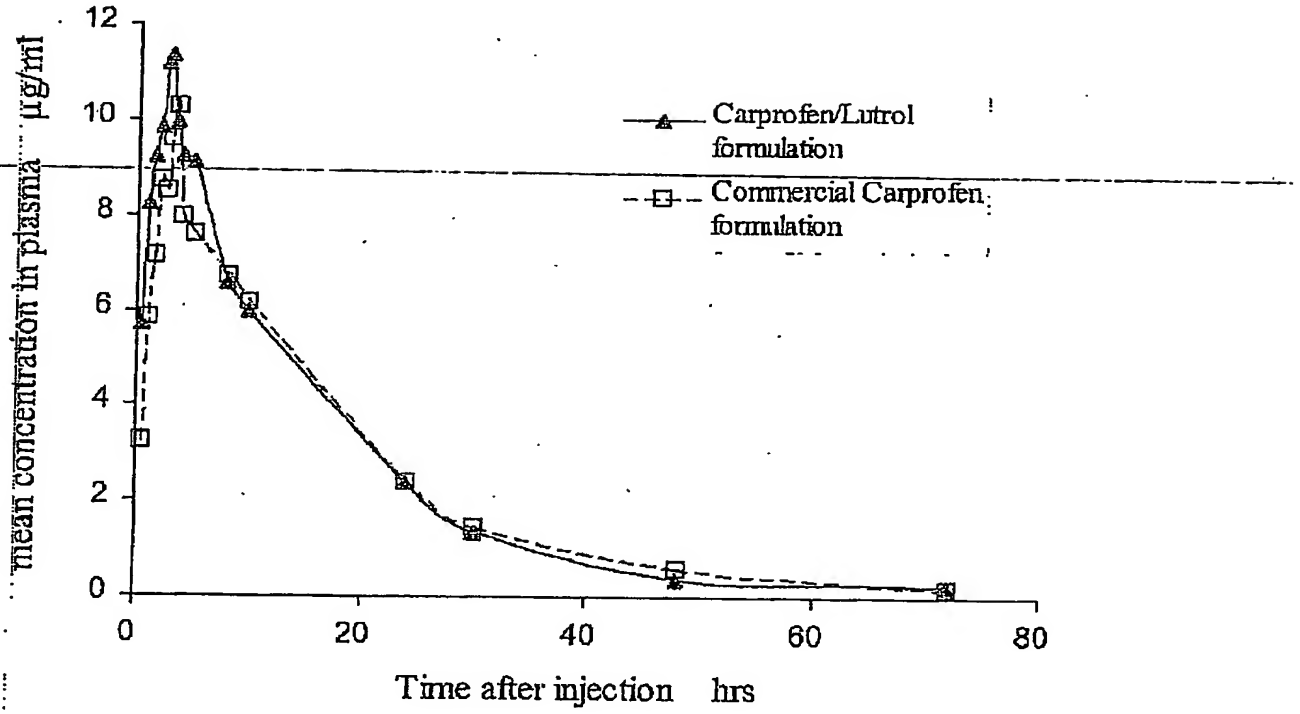
A study was undertaken with a view to evaluating the mean levels of carprofen found in dogs following the administration of a dose of approximately 4 mg/kg of a composition according to the Example in comparison with results obtained by administration of a commercially available product of comparable strength.

The results of the pharmacokinetic study are tabulated below and shown graphically in Figure 1. The Table compares the mean plasma concentrations of carprofen found in dogs after subcutaneous injection of carprofen at a dose of approximately 4mg/kg using a commercially available formulation, and using the formulation given in the Example. Statistical analysis of these results confirmed bioequivalence in accordance with European Guidelines (Volume 8 of EMEA/CVMP/016-00/Final).

Table 1

Time after injection (hours)	Carprofen/Lutrol formulation (µg/ml)	Commercially available Carprofen formulation (µg/ml)
0.5	5.73	3.27
1	8.24	5.86
1.5	9.24	7.16
2	9.85	8.76
2.5	11.18	8.53
3	11.36	9.63
3.5	9.94	10.29
4	9.23	7.99
5	9.12	7.6
8	6.57	6.75
10	5.98	6.18
24	2.39	2.41
30	1.37	1.48
48	0.39	0.6
72	0.23	0.18

Figure 1


mean concentration in plasma µg/ml
12
10
8
6
4
2
0
0
20
40
60
80
Time after injection hrs
Carprofen/Lutrol formulation
Commercial Carprofen formulation

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